

# Population-Based Case-Control Study on Cancer Screening

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Matched case-control studies have recently been used to evaluate the effectiveness of cancer screening. They enable us to estimate the odds ratios of dying of cancer or of getting invasive cancer. The study compares people with various patterns of screening history with those who were not screened. Criteria for eligible cases, controls, and screening histories that are compared as exposures are discussed. The results from a case-control study for evaluating screening for cervical cancer are shown as an example. Also, a study design of a case-control study for evaluating lung cancer screening in Japan is discussed, along with biases and applications of case-control studies in evaluating cancer screening.

## Introduction

In order to evaluate the effectiveness of cancer screening, various types of approaches have been developed (Table 1). As recommended in the 1983 Union Internationale Contre le Cancer (UICC) workshop, a randomized controlled trial should be the first choice (1). However, such a trial is sometimes difficult to conduct because of financial or ethical problems or timing in conducting the study (2). In these situations, nonexperimental studies should be chosen, although the interpretation of the results should be carefully checked in terms of various types of biases. Nonexperimental studies can be divided into two groups. One is a group-based

comparison between areas with different screening intensity. In these studies, a comparison can be done before and after the screening is introduced in the same population or between different areas with different screening intensities. Also, the correlation can be calculated between screening intensity and mortality or the incidence of the cancer. The other type of approach is an individual-based comparison between people screened and those who were not. In this type of study, either a prospective or retrospective approach can be applied, case-control studies fall into this category.

A case-control study was first applied to the evaluation of cervical cancer in Toronto (3). Since then, several case-control studies have been conducted for evaluating cervical cancer (4-7), breast cancer (8-10), stomach cancer (11), and lung cancer (12). Methodological problems have been discussed in terms of the definition of the cases, controls, and exposures to be compared (13-16).

## Definition of Cases, Controls, and Exposures

Before discussing the criteria for eligible cases and controls, it is necessary to define what outcomes should be measured when evaluating the effectiveness of cancer screening (15). When most of the cancers that are detected by screening are invasive cancers, the aim of the screening is to reduce the mortality of the cancer. In this case, the mortality of the cancer is the outcome. Screening for cancers of the breast, lung, and most of the other malignancies can be classified as this type.

On the other hand, when most of the cancers that are detected by screening are preinvasive cancers, the aim of the screening is to reduce the incidence of the invasive

Table 1. Classification of approaches for evaluating cancer screening.

Experimental study (randomized controlled trial)
Nonexperimental study
Group-based comparison between areas with different screening intensity
Time trend
Geographic difference
Correlation study
Individual-based comparison between screened and nonscreened people
Cohort study
Case-control study

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cancer as well as to reduce the mortality of the cancer. In this case, the incidence of the invasive cancer as well as the mortality can be the outcome to be measured. If the incidence of the invasive cancer is used, it can be measured earlier than the mortality, and also lead time bias and length bias can be avoided. Screening for cervical cancer and stomach cancer can be classified as this type.

In a matched case-control study for evaluating cancer screening, case series should include all deaths or all patients of invasive cancer in a defined population, and controls should be chosen from anyone at risk of the cancer in the same population who was alive with no previous diagnosis of the cancer at the time of the diagnosis of the matched case. Controls chosen from the patients with early stage disease, or people who died at the same time as the case, will not be appropriate; these selections have already been discussed in previous papers (13-15). In order to ensure the comparability between case and controls, it is necessary to match for the time period in which the screening histories were compared, as well as sex, age, and other confounding factors. According to the type of outcome measured, two kinds of situations have to be considered separately.

When using mortality of the cancer as the outcome, screening histories should be compared between case and controls up to the time of diagnosis of the case, including the screening that led to the diagnosis of the case (Fig. 1). Therefore, if a patient is detected by screening and then died of the cancer, he or she is classified as screening positive. If a patient is diagnosed with cancer in the early stages and thought to be cured, then he or she can be a control as long as the criteria for eligibility are satisfied. The period to compare the screening histories can be the full period from the time when screening started, or a defined period, such as 2 years or 10 years, backwards from the time diagnosing the case. The number of years since the last screening test and the number of screening tests within a defined period can also be used as exposure variables.

When using the incidence of invasive cancer as the outcome, two kinds of cases should be considered separately according to how the cases were detected: one is prevalent cases, detected by screening, and the other is incident cases, detected by symptoms. For prevalent cases, controls should be chosen from those who were

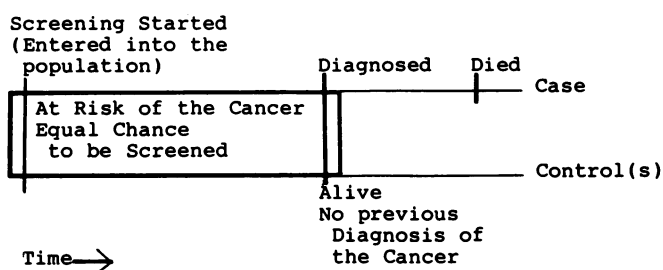


FIGURE 1. Definition of exposure when mortality is used as outcome. Includes all screening tests performed up to the time of diagnosis of the matched case, including the test that led to the diagnosis of the matched case.

screened at the time of diagnosis of the case, as shown in Figure 2. This matching ensures that controls are chosen from those people who do not have preinvasive cancer. Screening histories should be compared up to the time of diagnosis of the case, excluding the screening that led to the diagnosis of the case because it is used for matching. The period in which to compare screening histories can be defined as that when mortality was used as the outcome. It is better to limit the screening histories to those that resulted as negative if the specificity of the screening test is considerably high.

On the other hand, for incident cases, controls should be chosen from those who were not screened at the time of diagnosis of the case (Fig. 3). This is because incident cases were not screened at the time of their diagnoses by definition, so controls also should be chosen from those who were not screened at the time of diagnosing the case. Screening histories should be compared up to the time of diagnosis of the case, excluding the screening that led to diagnosing the case, just as for prevalent cases.

A typical tabular presentation of the result obtained in a case-control study for evaluating cancer screening is shown in Table 2. The odds ratio should be calculated using matched analysis (17). If other confounding factors that are not used as matching factors have to be controlled, an analysis by conditional logistic regression model should be used, including those variables in the model (16).

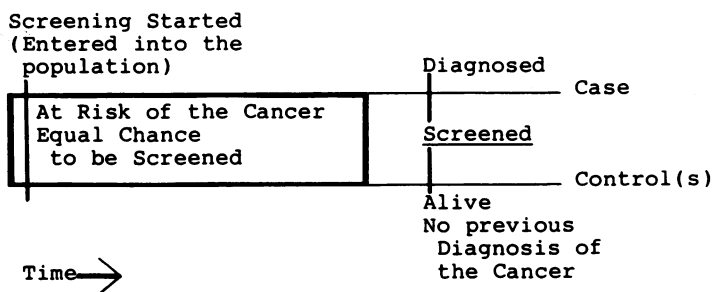


FIGURE 2. Definition of exposure when incidence of invasive cancer is used as outcome (prevalent case). Includes all screening tests performed up to the time of diagnosis of the matched case, excluding the test that led to the diagnosis of the matched case.

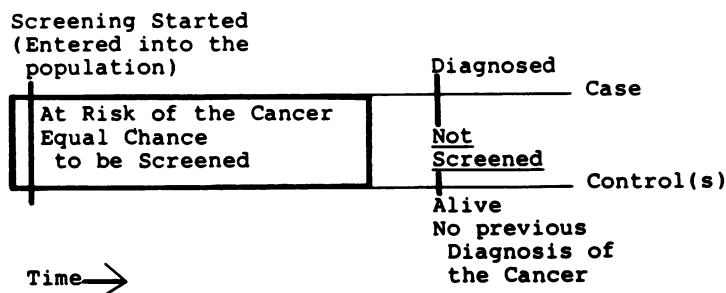


FIGURE 3. Definition of exposure when incidence of invasive cancer is used as outcome (incident case). Includes all screening tests performed up to the time of diagnosis of the matched case, excluding the test that led to the diagnosis of the matched case.

**Table 2. Presentation in a case-control study for evaluating cancer screening.**

Case	Number of controls screened in each matched set					Total
	0	1	2	.....	N	
Screened	m0	m1	m2	.....	mN	m
Not screened	n0	n1	n2	.....	nN	n

**Table 3. Results of cervical cancer screening in Nose Town, Japan, 1965–1987.<sup>a</sup>**

Period	Person-year of women over 30 years of age	Person-year of cases	Screening rate, %
1965–1969	13,460	689	5.1
1970–1974	14,639	1,336	9.1
1975–1979	15,188	1,170	7.7
1980–1983	13,099	1,060	8.1
1984–1987	13,933	1,859	13.3

<sup>a</sup> From Sobue et al. (18).**Table 4. Age distribution of cervical cancer cases.<sup>a</sup>**

Age <sup>b</sup>	Incidence		Mortality <sup>d</sup>
	Invasive	CIS <sup>c</sup>	
30–39	3(1) <sup>e</sup>	3(3)	0
40–49	8(5)	2(2)	1
50–59	7(0)	3(2)	4
60–69	5(0)	0(0)	5
70–79	5(1)	0(0)	5(1)
Total	28(7)	8(7)	15(1)

<sup>a</sup> From Sobue et al. (18).<sup>b</sup> Age at the time of diagnosis.<sup>c</sup> CIS, carcinoma *in situ*.<sup>d</sup> Observed up to February 1, 1988.<sup>e</sup> Screen-detected cases in parentheses.

## Results from a Case-Control Study for Evaluating Cervical Cancer Screening in Osaka, Japan

Nose Town, located in the northern rural area of Osaka Prefecture, has a highly stable population of about 10,000. Cervical cancer screening has been conducted in Nose Town since 1965. Table 3 shows both the person-year of women 30 years of age or more and the person-year of persons screened and the screening rate in Nose Town in a 4- or 5-year period. Screening rates were less than 10% until 1983, and they increased to 13% between 1984 and 1987. In order to evaluate the effectiveness of the cervical cancer screening program, a case-control study was conducted.

Table 4 shows the age distribution of all cervical cancer cases and those who died of the disease. There were no deaths in carcinoma *in situ* cases up to February 1, 1988. Cases who were under 29 years old or over 80 years old were excluded. There were 28 patients with invasive cancers and 15 patients had died of cervical cancer; these patients were used as case series. Controls were chosen from those who were alive with no previous diagnosis of the cancer at the time of the diagnosis.

Detailed methods of data collection have been described elsewhere (18).

Table 5 shows the result of the matched case-control comparison when mortality was used as the outcome. Exposure is defined by whether or not the patients have been screened at least once within 10 years up to the year the case was diagnosed. Case and controls were matched by the year of birth, and 10 controls for each case were chosen from the computer file of residents in 1965 when the screening started. Only one dead case in the files was screened. The odds ratio of dying of cervical cancer for screened versus nonscreened women was estimated as 0.22.

Table 6 shows the result of the matched case-control comparison when incidence of invasive cancer was used as the outcome. For screen-detected cases, i.e., prevalent cases, controls were chosen from those who were screened at the time of the diagnosis of the case. For symptom-detected cases, i.e., incident cases, controls were chosen from those who were not screened at the time of diagnosis. For one particular screen-detected case, only 2 controls were available, otherwise 10 controls for each case could be chosen successfully. The odds ratio of getting invasive cancer for screened versus nonscreened women was estimated as 0.43 for screen-detected cases and 0.41 for incident cases. The odds

**Table 5. Distribution of matched sets of dead cases and their controls according to screening history.<sup>a</sup>**

1:10 Match	Number of matched controls screened											
Case	0	1	2	3	4	5	6	7	8	9	10	Total
Screened	1	0	0	0	0	0	0	0	0	0	0	1
Not screened	6	2	1	1	1	0	2	1	0	0	0	14

<sup>a</sup> From Sobue et al. (18). Odds ratio = 0.22 (95% CI = 0.03–1.95)**Table 6. Distribution of matched sets of invasive cancer cases and their controls according to screening history by sets of screen-detected and symptom-detected cases.<sup>a</sup>**

Sets of screen-detected cases				
1:2 Match	Number of matched controls screened			
Case	0	1	2	Total
Screened	0	0	0	0
Not screened	1	0	0	1

	Number of matched controls screened										
1:10 Match	0	1	2	3	4	5	6	7	8	9	10
Screened	0	0	0	0	0	0	0	0	0	3	1
Not screened	0	0	0	1	0	0	0	1	0	0	0

OR = 0.43 (95% CI = 0.05–3.71)

Sets of symptom-detected cases											
	Number of matched controls screened										
1:10 Match	0	1	2	3	4	5	6	7	8	9	10
Screened	0	0	2	0	0	1	0	0	0	0	3
Not screened	6	3	2	0	2	1	2	2	0	0	18
OR = 0.41 (95% CI = 0.11–1.56)											

OR = 0.41 (95% CI = 0.11–1.56)

<sup>a</sup> From Sobue et al. (18). OR, odds ratio. OR for both groups combined = 0.41 (95% CI = 0.13–1.29)

**Table 7. Odds ratios (OR) of getting invasive cancer according to the number of screening tests within 10 years.<sup>a</sup>**

Number of tests within 10 years	OR	95% CI
None	1.00	
Once	0.54	0.18 – 1.65
Twice or more	0.11	0.01 – 1.06

<sup>a</sup>From Sobue et al. (18).  $\chi^2$  for linearity = 4.06 ( $p < 0.05$ )

ratio for screen-detected cases is thought as an odds ratio for prevalence, and the odds ratio for symptom-detected cases as the odds ratio for incidence. If the invasive period of the detectable preclinical phase is almost equal to the unit of time, a year in this case, then these ratios will be very similar and both types of sets can be combined. The odds ratio for both groups combined was estimated at 0.41.

Table 7 shows the odds ratios of getting invasive cervical cancer according to the number of screening tests within 10 years. Compared to those patients who had never been screened, the odds ratios for being screened once was 0.54, and being screened twice or more was 0.11. The trend for the linearity was statistically significant.

Table 8 shows the odds ratios according to the number of years since the last screening test. The odds ratios for being screened 1 to 2 yr before was 0.27, 0.23 for 3 to 4 years, and 0.55 for 5 years or more.

Summarizing these findings, it was estimated that 78% of cervical cancer mortality and 59% of invasive cervical cancer incidence among nonscreened women could be prevented by cervical cancer screening. The main problem of this study is all the estimated odds ratios were not statistically significant. For example, the power to make odds ratio of dying of cervical cancer statistically significant with 5% alpha error is 64%. In order to make this power 80%, an additional 10 sets are needed. In this town, however, about one or two deaths of cervical cancer have been observed per year recently, so that we would have to follow 10 more years in order to obtain statistically significant results. Considering these facts, we decided to publish the report, emphasizing how the biases can be reduced in this study.

## Study Design of a Case-Control Study for Evaluating Lung Cancer Screening in Japan

Lung cancer screening by chest X-ray for all participants and sputum cytology for high-risk people have been conducted for several years in some areas in Japan, although the effectiveness of lung cancer screening on the reduction of the mortality has never been established. The results obtained from three randomized controlled trials conducted in the U.S. showed that the effectiveness of sputum cytology for high-risk groups is minimal, if any, but the effectiveness of chest X-rays

**Table 8. Odds ratios (OR) of getting invasive cancer according to the number of years since the last screening test.<sup>a</sup>**

Years since last test	OR	95% CI
None	1.00	
1–2	0.27	0.06 – 1.23
3–4	0.23	0.02 – 2.24
5 or more	0.55	0.13 – 2.29

<sup>a</sup>From Sobue et al. (18).  $\chi^2$  for linearity = 3.36 ( $p < 0.10$ ).

was not directly investigated. The results from a case-control study conducted recently in Berlin, DDR, showed no reduction of mortality of lung cancer in those who were screened by chest X-ray. However, since the histologic distribution is different in the DDR and Japan and since the level of medical technology may also be different between the two countries, results in the DDR may not be applied directly to Japan. It is also true, however, that an evaluation of lung cancer screening in terms of mortality reduction has never been conducted in Japan.

Looking at these facts, a case-control study for evaluating lung cancer screening was started last year with the support of Grants-in-Aid for cancer research from the Ministry of Health and Welfare of Japan. The problems when conducting a case-control study for evaluating screenings for lung cancer are as follows: first, the screening procedure is complicated and usually a chest X-ray is taken for all cases and sputum cytology is performed, only for high-risk groups; second, lung cancer is a heterogeneous disease in terms of various characteristics, and these may have to be divided into subgroups when evaluating; third, chest X-ray examination is available in various facilities, so it is difficult to collect complete information of the exposure; fourth, the expected mortality reduction by screening may be small, so a larger number of subjects are needed; and finally, smoking can be a strong confounding factor.

In the current Japanese case-control study for evaluating lung cancer screening, cases are defined as all patients who died from lung cancer between the ages of 40 and 74. These cases were diagnosed after the screening started and had lived in their area since the year the screening started. Also, cases were limited to high-risk groups for men and nonhigh-risk groups for women to increase the efficiency of the study. Controls were defined as anyone alive at the time of diagnosis of the matched case who had no previous diagnosis of lung cancer before the case was diagnosed, and who lived in their area since the year the screening started. Also controls were matched by sex, year of birth, and whether they were a high-risk group or not. High-risk groups were defined either as those who smoked cigarettes 20 pack-years and who were 40 years old or more, or those who smoked cigarettes 30 pack-years and who were 50 years old or more. These criteria were actually

used for selecting people for sputum cytology in each study area. Concerning the calculation of the sample size, in order to make the odds ratio of 0.75 statistically significant with 5%  $\alpha$  error and 20%  $\beta$  error, we estimated that 600 cases with 5 controls for each case would be needed, assuming a 30% screening rate in a population. So far, about 100 cases have been registered in the study and results will be available at the end of 1990.

## Biases and Applications of a Case-Control Study for Evaluating Cancer Screening

Lead time bias and length bias are the basic problems when survival is compared between screen-detected and symptom-detected cases, and they should be considered also in a case-control study (19). Lead time is defined as the interval between the time of detection by screening and the time at which the disease would have been diagnosed in the absence of screening. It makes survival in screen-detected cases look better, even if in effect there is no difference. In case-control studies where mortality is used as the outcome, a lead time bias exists; it makes the odds ratio lower if the survival of the cases are observed only for a short period. If the survival of most cases is observed for a sufficiently long period this bias can be reduced. When the incidence of invasive cancer is used as the outcome, a lead time bias does not exist. On the other hand, a length bias refers to the fact that screening tests tend to detect the slow-growing cancers selectively and miss the rapid-growing cancers that are more likely to present symptoms between screening examinations. In case-control studies, patients who were diagnosed before the screening program started should be excluded from the case series because they did not have any chance to be screened. These patients tend to undergo a long interval between diagnosis and death; this means there is a better prognosis of the disease. Therefore, after excluding these patients eligible cases may include those who have rapidly growing cancers. Therefore, if the study period used to collect cases is too short, the odds ratio will be biased towards unity; this situation is unfavorable for screened people. This type of bias also can be reduced if the study period that is used to collect cases is sufficiently long. Also, when using the incidence of invasive cancer as the outcome, this type of bias is not a concern.

There are various sources for the selection bias, which means different characteristics causing differences in the mortality or incidence between screened and non-screened people. First, if risk factors for the cancer are distributed differently between screened and non-screened people, the mortality or incidence cannot be simply compared in terms of the effectiveness of the screening. For example, participants in cervical cancer screening tend to have higher socioeconomic status,

while low socioeconomic status is one of the risk factors for cervical cancer. Therefore, the incidence of cervical cancer is already lower in screened women, even if no effect from screening exists. However, as long as the factors are known and related information can be obtained in the study, this bias can be practically controllable. Controls are taken by either matching the collection of data or adjusting the analysis because the number of subjects dealt with in a case-control study is usually small. Secondly, besides the incidence itself, the characteristics of the cancer may be different between screened and non-screened people. For example, smoking is an established risk factor for lung cancer and increases the incidence of the disease. Also, smoking is related to each histologic type; namely, it has a strong relation to squamous and small cell carcinoma and a weak relation to adenocarcinoma. Therefore, the histologic distribution can be different between screened and non-screened people if the rate of smoking is different between screened and non-screened people. Again, this is also practically controllable as long as the information can be obtained. Third, since participants for screening tend to be health-conscious, they may seek medical care earlier than nonparticipants do when they have clinical symptoms. This may lead to overestimation of the effect of the screening. Also, the prognosis of the cancer may be different because of the more careful lifestyle of the screened people. These types of biases cannot be controlled in a study design itself and additional information will be needed.

There are also various types of misclassification on outcome and exposure, which can happen in a case-control study. Misclassification on the outcome can occur as a false-positive case or a false-negative case. False-positives cases occur if the diagnosis of the cancer is more selectively applied to screened people. In order to avoid this misclassification, cases should be carefully reviewed to determine whether or not the clinical course is compatible with the cancer. On the other hand, false-negative cases occur if the diagnosis of the cancer is missed selectively in non-screened people. This is rather difficult to deal with and additional information such as autopsy data will be needed from outside the study.

Misclassification on the exposure can occur as recall bias, which is one of the most important biases to control in case-control studies. Recall bias means that cases are more likely to recall some past exposure rather than healthy controls. Besides this bias, it is often difficult to recall an exact past screening history for both cases and controls. Therefore, it is preferable to use the list of cases stored in the medical facilities rather than the data obtained from an interview. This measure can prevent these problems, but conversely, screening tests conducted in other facilities will be ignored. This type of problem can be reduced if areas where few facilities are involved in the screening test are chosen for study.

Summarizing the points discussed above, the merits and drawbacks of a case-control study for evaluating screening are listed compared to other types of ap-

proaches, such as randomized controlled trials. The merits of using a case-control study are as follows: results are quickly available; the studies are applicable for screening that is already widespread; fewer ethical problems arise when compared to experimental studies; a large number of study subjects are not needed, such as in the cohort approach; and it is possible to control known confounding factors as long as the related information is available. Also, it is appropriate to evaluate exposures occurring close to the outcome; screenings that take place closer in time to the outcome are more effective, and a retrospective approach can evaluate these exposures easily. This makes it possible to evaluate optimal screening intervals from a case-control study. On the other hand, there are also drawbacks in a case-control study: the study is influenced by the condition of maintenance of the past screening records, and it is sometimes difficult to choose appropriate controls; also, it is impossible to control unknown confounding factors.

A case-control study for evaluating screening can be applied to various kinds of situations. It can be used to evaluate the effectiveness of screenings that are already widespread to find an optimal screening schedule after the effectiveness is established, or to monitor the quality of routine screening activity.

Recently, case-control studies are used more frequently in various fields including the evaluation of cancer screening. Although many methodological problems remain to be discussed, there are also sufficient reasons for promoting the use of case-control studies for evaluating screening in the future.

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